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Inadequate immunity to measles in children vaccinated at an early age: effect of revaccination

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This report describes a follow-up serological study of 79 Brazilian children who, because of their young age, had failed to develop protective levels of immunity after vaccination against measles. There was serological evidence that infection with wild virus had occurred at a rate of about 17% per annum. Approximately 1½ years after the initial vaccination, 46% of the uninfected children maintained very low levels of neutralizing antibody, but did not have a measurable haemagglutination-inhibition titre. Revaccination did not elicit an IgM response in most children, but stimulated anti-measles IgG production in all of them. In 36% of the children, the IgG titres fell again within three months to levels that may permit reinfection. If it is assumed that some of the persistent titres can be attributed to wild virus infection, the actual effect of revaccination would have been to immunize no more than 60% of the susceptible group. The results suggest that early administration of measles vaccine may produce a cohort of children with inadequate immunity who cannot be fully immunized by revaccination. The implications of these findings for measles immunization programmes are discussed.

In 1973, Linnemann et al. (*1*) and Cherry et al. (*2*) showed that many children who failed to respond to live measles vaccine with protective titres of antibody, because of residual maternal antibody, nevertheless received a primary immunological stimulus. This stimulus modified the response to subsequent infection in that unusually high titres of IgG were produced initially, and the disease itself was often mild. Arbeter et al. (*3*) showed that the serological response to revaccination in these children was also different from that in children with no prior immunization. These early reports have been confirmed by several subsequent studies (*4–9*, J. Polkowski et al., personal communication, 1982), which have also shown that antibody titre in reimmunized children may fall, after several months, to very low levels (*8*) and that children vaccinated twice may still experience clinically recognizable measles (*9*). Thus, there is ample evidence that the presence of low levels of maternal antibody at the time of vaccination may interfere with the response to revaccination, leaving the child susceptible to wild virus disease, albeit usually in a milder form than might otherwise have occurred. This state in which a child is immunologically sensitized, but not immune to infection, we shall call "inadequate immunity".

Because many children in developing countries contract measles before their first birthday and because the measles mortality rate is high in this age group, it is recommended practice in these areas to give measles vaccine at an age when a considerable proportion of the recipients still have sufficient maternal antibody to block a full immune response. In these countries, therefore, a substantial number of children develop inadequate immunity.

The present report describes an immunological study in a developing country to examine the response to revaccination in children who were first vaccinated in 1979 without seroconversion, when they were less than 12 months old. The results of the initial vaccination study have already been reported (*10*). Four weeks after primary immunization of 2042 seronegative children, 1672 had acquired adequate antibody titres. It should be recognized that most of the

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vaccine failures in the original study occurred in children aged under 9 months; the seroconversion rate in children aged 9–12 months was 91.9%.

MATERIALS AND METHODS

Subjects

The present study was carried out in three economically diverse states of Brazil: Pará, Pernambuco, and Rio Grande do Sul. In addition to the children vaccinated in 1979, we also included 17 children from the same areas who were vaccinated in 1980, according to the same protocol, with the Biken CAM-70 strain of vaccine (*11*). Our target population thus consisted of 248 children, who had lacked measurable prevaccination antibody and had failed to seroconvert, i.e., they had measles haemagglutination-inhibition (HI) antibody titres of less than 10, four weeks after vaccination. In August 1981, 79 of these children were located and tested for measles immunity; 10 of these children had been over 9 months old when first vaccinated. Eleven other children were located, but their parents did not grant permission for a blood sample to be taken. The other 158 children were not found; some had moved, some lived in remote areas, and for some the house address was inadequate. Of the group sought, 23% had been over 9 months old when first vaccinated; 13% of those found were in this age category.

Of the children retested, 42 had already been revaccinated; the remainder were revaccinated with Attenuvax strain[a] at the time they were contacted. (In Brazil, each child must have a vaccination record to be eligible for child-support payments, so records of vaccination dates were good.) The distribution of the children, by age at vaccination and interval between vaccinations, is given in Table 1. In three instances, the mother reported that the child had had measles since the first vaccination and, in one instance, after the second vaccination. These cases could not be confirmed and have not, therefore, been distinguished in the analysis.

Immunological techniques

Because we anticipated that many of the responses to revaccination would be secondary in nature and hence accelerated, serum samples were collected 3 weeks after revaccination, instead of the more usual 4 weeks.

Haemagglutination-inhibition tests were performed as described previously (*12*). IgM titre was taken as the difference in titre before and after treatment with 2-mercaptoethanol (1 mol/litre), after extraction of the serum with staphylococcal A protein. This difference was considered significant if it amounted to more than 20% of the pre-extraction total. Neutralization (NT) tests were carried out with virus that had been plaque-purified to remove defective particles. The virus was incubated with 2-fold serum dilutions, between 1:2 and 1:256, for 1 hour at room temperature. Vero cell cultures grown in 7-mm diameter wells were then inoculated with 10 plaque-forming units of virus.

[a] Merck Sharp Dohme, West Point, PA, USA.

Table 1. Distribution of subjects by age at first vaccination

Interval between vaccinations (months)	Age at first vaccination (months)						Total
	5	6	7	8	9	10–12	
4–6	0	2	1	1	0	0	4
6–12	1	16	12	3	1	1	34
12–18	0	1	6	5	1	1	14
18–24	1	8	5	0	5	0	19
24–26	0	3	0	2	3	0	8
Total	2	30	24	11	10	2	79

RESULTS

Serological status prior to revaccination

At the time the children were contacted for follow-up, 17.5 ± 6.4 months after primary vaccination, 37 had no history of revaccination. Nine of these children had an HI titre of 10 or more (Table 2). Their antibody levels had thus increased from $\leqslant 5$ to $\geqslant 10$ subsequent to the tests conducted four weeks after the first vaccination, over a period when titres usually fall 2-fold. We believe that these increases in titre were the result of intercurrent infection. They indicate an infection rate of 17% per annum; this is low for a developing country, but explicable by the fact that the children lived in communities where vaccination efforts had been intensified. All children with positive HI tests also had positive neutralization reactions.

Eleven other children did not have detectable HI antibody but had low positive NT titres. Since neutralization titre was not measured when these children were originally classified as vaccine failures, we cannot determine if their status in this respect had changed; these very low neutralization titres may be attributable to the first vaccination.

Table 2. Antibody titres 10–25 months after primary unsuccessful measles vaccination, before and 3 weeks after revaccination

Antibody status before revaccination		No. of children	GMT[a] before revaccination		GMT[a] after revaccination	
HI	NT		HI	NT	HI	NT
> 5	⩾ 20	6[b]	45	155	33	105
⩽ 5	2–20	11		4.1	34	247
⩽ 5	< 2	8			60	280

[a] Geometric mean titre.

[b] Three other children had an HI titre > 5 and an NT titre ⩾ 20 before revaccination; their post-revaccination titres were not measured.

Serological status three weeks after revaccination

Six children whose HI titres had been 10 or higher before revaccination showed no response to revaccination (Table 2). All the other children, including those with very low NT titres, responded serologically to revaccination. Only 2, however, had significant anti-measles IgM, and in these, this antibody accounted for less than one-third of the total post-revaccination titre. The geometric mean titre (GMT) of HI antibodies in these sera was similar to that found in children from the same areas four weeks after primary vaccination (*10*). NT titres also increased in all members of this group, and showed a GMT of 261. This may be compared with a value of 67, four weeks after initial vaccination with CAM-70 vaccine in 172 children who responded at that time (S. Ueda, personal communication, 1980).

Serological status several months after revaccination

A total of 42 children were studied 3–17 months after revaccination (Table 3). The mean interval between vaccine doses was 9.5 months (± 5.0 months, standard deviation), and the mean time since revaccination was 12.0 months. There was no apparent relationship between titre and either of these time intervals, and the data have therefore been pooled.

Table 3. Measles antibodies in children 3–17 months after revaccination

	HI titre		NT titre	
	No. tested	GMT	No. tested	GMT
Inadequate titre[a]	15		12	8.9
Protected from infection	27	24.5	28	96.8

[a] HI < 5 or NT < 20.

Fifteen (36%) of these children lacked protective levels of antibody.

The children lived in the same geographic areas as the 37 unrevaccinated children discussed above. It is probable, therefore, that the two groups were subject to similar rates of intercurrent infection with wild virus. If so, at least 5 members of this group would have been exposed to infection and it is probable, therefore, that fewer than 22 of the 27 positive titres were attributable to revaccination.

There are few data on which to base an estimate of the NT titre required to protect from infection. Tentatively, on the basis of the observation that children with an NT titre of 16 or less responded to revaccination with a substantial boost in titre (a response which would require replication of the vaccine virus), we assume that an NT titre greater than 20 is needed to prevent infection. This may be a minimum value because virulent virus may be more infectious than the vaccine strain used to determine immunity thresholds. On this basis, the proportion estimated as remaining susceptible (30%) agrees well with that indicated by the HI test.

DISCUSSION

We have become accustomed to consider an HI titre of less than 10, four weeks after vaccination, as indicative of vaccine failure (*10*, *13*), and indeed, this level does correspond approximately with the borderline for resistance to disease (*2*, *14*). However, in the present study, nearly all children who received vaccine were, in fact, sensitized to measles antigens. Two years later, many had low levels of neutralizing antibody, which were not high enough to block replication of vaccine virus and consequent restimulation. With the techniques used here, in which IgG_1, IgG_2, and IgG_4 are removed before testing for IgM, a very high proportion of primary reactors were shown to be

positive for IgM during the early phase of response (*9*). The previously vaccinated children produced little or no IgM when restimulated. The IgG titres produced in response to revaccination were poorly maintained, and many fell back to very low levels after a few months. The question of how often infection causes recognizable disease in these sensitized persons, and how severe this disease may be, is beyond the scope of this study. From earlier studies, it is clear that revaccination reduces the incidence of apparent disease (*14*) but does not always prevent it (*9*).

Immunity to measles can be a very firm state, unaffected by exposure to the virus (*6*, *15*, *16*). The primary aim of vaccination against measles is to induce the same kind of solid, lifelong immunity as that which ordinarily follows natural disease. However, the immunity induced by vaccination may be a tenuous condition which may modify but not prevent infection; this possibility has often been overlooked in the past. Low levels of immunity follow exposure to virus in the presence of low levels of passively acquired antibody, whether that antibody is maternal, as in this study, or acquired by injection (*17*).

In some important respects, recognition of inadequate immunity is encouraging from the point of view of the efficacy of vaccination. Many children who were considered to be unprotected are not, in fact, likely to experience severe forms of the disease, and it can be expected that overall mortality rates will be reduced more than would be suggested by the proportion of children showing seroconversion. Reduced virus excretion by these subjects has not yet been demonstrated, but is a strong possibility, by analogy with the modified disease seen in persons given immune globulin by injection (*17*). If these patients do shed less virus, they will not play the same role as unmodified cases in virus transmission.

On the other hand, recognition of inadequate immunity raises problems. Revaccination of children who have been unsuccessfully immunized may not yield the solid immunity that could have been attained if the first dose had been delayed (*9*, *15*, J. Polkowski et al., personal communication, 1982). Even if children with inadequate immunity can be protected by multiple vaccinations, it seems probable that many will end up with very low antibody titres. Those in this category who become mothers will have very little antibody to pass to their offspring, and measles infections in infants under six months of age could become more frequent in the future. The possibility that infection with wild virus may not produce lasting immunity in these children must also be considered. Rare second and third episodes of measles have been reported (*18–20*), and may be explained in terms of inadequate immunity resulting from an initial infection contracted while the child retained borderline levels of passive antibody. If this is indeed the case, such reinfections may become more common in areas where vaccine is given early.

Vaccination at 9 months of age protected 88% of subjects in a large representative study (*10*). For the present, the important point is that this procedure protects nearly 9 out of every 10 recipients. For the future, however, we must be concerned that the 10% who are unprotected will be sufficient to maintain measles endemicity, even if 100% vaccine coverage is attained. The number of unprotected children can be further reduced by revaccination, but not to such low levels as might have been achieved if the first dose had been delayed. During the early stages of vaccination programmes in many developing countries, early measles cases and deaths are too numerous to permit the recommended age for vaccination to be higher than 9 months. However, one result of a successful programme is a shift of cases to older age groups (*20*, *21*). The authors of this report suggest that, when such a change in age-specific attack rates becomes apparent, consideration should be given to raising the age for vaccination.

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RÉSUMÉ

IMMUNISATION INADÉQUATE CONTRE LA ROUGEOLE CHEZ DES ENFANTS VACCINÉS EN BAS ÂGE: EFFET DE LA REVACCINATION

Un groupe de 37 enfants qui avaient été vaccinés sans succès contre la rougeole avant l'âge d'un an ont été soumis à de nouvelles épreuves un an et demi plus tard environ. L'examen sérologique a montré que neuf d'entre eux avaient été infectés par la rougeole dans l'intervalle; chez la moitié des autres à peu près, le titre d'anticorps neutralisant

était très faible. A la revaccination, tous les enfants qui n'avaient pas déjà contracté la rougeole ont présenté une réponse sérologique, mais presque toujours sans composante IgM.

Chez 42 enfants, on a de nouveau recherché la présence d'anticorps de la rougeole entre 3 et 17 mois après la revaccination. Nous estimons qu'au moins 5 de ces enfants avaient certainement été en contact avec la rougeole sauvage depuis leur première vaccination. La moitié seulement des autres conservait un niveau protecteur d'anticorps attribuable à la revaccination.

Il apparaît donc qu'un groupe d'enfants, ayant été vaccinés trop précocement, ne possédaient qu'une immunité inadéquate et ne pouvaient être ultérieurement immunisés avec succès par la revaccination. Cependant, d'autres études ont montré que, si nombre de ces enfants ne peuvent être immunisés par les vaccins actuellement utilisés, ils sont d'ordinaire moins sévèrement atteints lorsqu'ils sont infectés par un virus sauvage que ceux qui n'ont reçu aucun vaccin.

REFERENCES

1. LINNEMANN, C. C. ET AL. Measles IgM response during reinfection of previously vaccinated children. *Journal of pediatrics*, **82**: 798-801 (1973).
2. CHERRY, J. D. ET AL. A clinical and serologic study of 103 children with measles vaccine failure. *Journal of pediatrics*, **82**: 802-808 (1973).
3. ARBETER, A. M. ET AL. Measles immunity: reimmunization of children who previously received live measles vaccine and gamma globulin. *Journal of pediatrics*, **81**: 787-741 (1972).
4. BASS, J. W. ET AL. Booster vaccination with further live attenuated measles vaccine. *Journal of the American Medical Association*, **235**: 31-34 (1976).
5. MEDICAL RESEARCH COUNCIL MEASLES VACCINE COMMITTEE. Clinical trial of live measles vaccine given alone and live vaccine preceded by killed vaccine. *Lancet*, **2**: 571-575 (1977).
6. DESADA-TOUS, J. ET AL. Measles revaccination. Persistence and degree of antibody titer by type of immune response. *American journal of diseases of children*, **132**: 287-290 (1978).
7. WILKINS, J. & WEHRLE, P. F. Additional evidence against measles vaccine administration to infants less than 12 months of age: altered immune response following active/passive immunization. *Journal of pediatrics*, **94**: 865-869 (1979).
8. LINNEMANN, C. C. ET AL. Measles immunity after revaccination: Results in children vaccinated before 10 months of age. *Pediatrics*, **69**: 332-335 (1982).
9. SMITH, F. R. ET AL. Reported measles in persons immunologically primed by prior vaccination. *Journal of pediatrics*, **101**: 391-395 (1982).
10. MINISTRIES OF HEALTH OF BRAZIL, CHILE, COSTA RICA AND ECUADOR, AND THE PAN AMERICAN HEALTH ORGANIZATION. Seroconversion rates and measles antibody titers, induced by measles vaccine in Latin American children 6-12 months of age. *Bulletin of the Pan American Health Organization*, **16**: 272-285 (1982).
11. OKUNO, Y. ET AL. Studies on further attenuated live measles vaccine. VII. Development and evaluation of CAM-70 measles virus vaccine. *Biken's journal*, **14**: 253-258 (1971).
12. BLACK, F. L. Measles virus. In: Lennette, E. H. et al., ed., *Handbook of microbiology*, 2nd ed., Washington, DC, American Society for Microbiology, 1974, pp. 709-715.
13. Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. Collaborative study by the Ministry of Health of Kenya and the World Health Organization. *Bulletin of the World Health Organization*, **55**: 21-31 (1977).
14. SHASBY, D. M. ET AL. Epidemic measles in a highly vaccinated population. *New England journal of medicine*, **296**: 585-589 (1977).
15. BECH, V. Studies on the development of complement fixing antibodies in measles patients. *Journal of immunology*, **83**: 267-275 (1959).
16. BRODY, J. A. ET AL. Measles vaccine field trials in Alaska. II. Vaccination on St. Paul Island, Pribilofs. *Journal of the American Medical Association*, **190**: 965-968 (1964).
17. BLACK, F. L. & YANNET, H. Inapparent measles after gamma globulin administration. *Journal of the American Medical Association*, **173**: 1183-1188 (1960).
18. CHERRY, J. D. ET AL. Urban measles in the vaccine era: a clinical, epidemiologic, and serologic study. *Journal of pediatrics*, **81**: 217-230 (1972).
19. SCHAFFNER, W. ET AL. Clinical epidemiology of sporadic measles in a highly immunized population. *New England journal of medicine*, **279**: 783-789 (1968).
20. HINMAN, A. R. Measles and rubella in adolescents and young adults. *Hospital practice*, **17**(10): 137-149 (1982).
21. BLACK, F. L. The role of herd immunity in control of measles. *Yale journal of biology and medicine*, **55**: 351-360 (1982).